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| 09/808,314 | 03/14/2001 | Randall W. Nelson | 41821.0236 | 3078 |

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| EXAMINER |
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COUNTS, GARY W

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| ART UNIT | PAPER NUMBER |
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1641

DATE MAILED: 08/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/808,314

Applicant(s)

NELSON ET AL.

Examiner

Gary W. Counts

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 20-33, 35-40, 42, 44-46 and 48 is/are pending in the application.
- 4a) Of the above claim(s) 1-14 and 20-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-33, 35-40, 42, 44-46 and 48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the claims

The amendment filed May 25, 2005 is acknowledged and has been entered.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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4. Claims 31-33, 35 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al (Direct Analysis of Affinity-Bound analytes by MALDI/TOF, Anal. Chem. 1994, 66, 2609-2613) in view of Gaskell (Quantification of steroid conjugates using fast atom bombardment mass spectrometry, steroids, 1990, vol. 55, pages 458-462).

Papac et al disclose a method for the Mass spectral identification and detection of analytes separated by immunoaffinity chromatography (abstract). Papac et al disclose antibody immobilized to agarose beads and used as affinity columns (p. 2611). Papac et al disclose combining a specimen with the beads to capture antigen present in the sample (post-combination affinity reagent). Papac et al disclose washing to remove any unbound antigen. Papac et al disclose that the sample is mixed with the beads and centrifuged and supernatant removed. Papac et al discloses that a matrix containing formic acid was added and the supernatant was tested by MALDI/TOF mass spectrometry (single dimension mass spectrometeromic analysis) (p. 2611, col 1 & p. 2613, col 2). Papac et al disclose determining the analyte by m/z (mass to charge ratio).

Papac et al (Anal Chem.) differ from the instant invention in failing to teach the specimen is combined with an internal reference species of known concentration prior to the capturing and isolation step wherein both the analyte and the IRS are captured and isolated. Papac et al also fails to teach quantifying the analyte.

Gaskell discloses quantifying an analyte, where a deuterated internal standard is added to a sample, which is then mixed with a solid phase incorporating bound

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antiserum for isolating the analyte and internal standard. Gaskell discloses that for quantification of the analyte, the analyte and internal standard are compared to a standard curve (p. 460). Gaskell discloses that the standard curve was obtained by analyses of standard mixtures of the analyte and the analyte analog. Gaskell further discloses that the addition of an internal standard provides for precise and accurate data (p. 459) and provides for the quantification of an analyte.

It would have been obvious to one of ordinary skill in the art to incorporate an internal standard and affinity reagents and also develop a standard curve for quantification analyses into the method of Papac et al (Anal. Chem). Because Gaskell teaches that the addition of an internal standard provides for precise and accurate data and provides for the quantification of an analyte of interest. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating an internal standard and affinity reagents as taught by Gaskell into the method of Papac et al.

5. Claims 37-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al in view of Gaskell as applied to claims 31-33, 35 and 36 above, and further in view of Chiabrando et al (Journ of Chromatography 495 (1989) 1-11).

See above for teachings of Papac et al and Gaskell.

Papac et al and Gaskell differ from the instant invention in failing to teach combining a plurality of distinctive internal reference species to the sample.

Chiabrando et al disclose adding multiple deuterated internal standards to a sample and also the use of immobilized antibodies to capture and isolate the analytes

and internal standards (internal reference) (p. 1). Chiabrando et al discloses that this provides for the simultaneous measurement of analytes and their metabolites (p. 2).

It would have been obvious to one of ordinary skill in the art to incorporate multiple internal standards as taught by Chiabrando et al into the modified method of Papac et al because Chiabrando et al discloses that this provides for the simultaneous measurement of analytes and their metabolites and further because it would have been obvious to one of ordinary skill in the art to use different types of standards with the different analytes to be detected.

6. Claims 44-46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papac et al and Gaskell in view of Chiabrando et al as applied to claims 31-33, 35-40 and 42 above, and further in view of Merren (US 3,770,337).

See above for teachings of Papac et al., Gaskell, and Chiabrando et al.

Papac et al (Anal. Chem.), Gaskell and Chiabrando et al differ from the instant invention in failing to specifically teach interpolating the analyte species mass spectrometric response to the IRS's mass spectrometric response.

Merren teaches the addition of reference substance which provides a spectrum containing peaks at several known mass-to-charge ratios. Merren teaches that the reference spectrum is accurately correlated with the spectrum of the unknown substance, therefore the reference peaks act as accurate markers forming a calibrated scale from which the mass-to-charge ratios of peaks of the unknown substance is interpolated. Merren teaches that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances, thereby

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permitting single channel processing of the combined signal (col 1, lines 53 – col 2, lines 19.

It would have been obvious to one of ordinary skill in the art to interpolating the analyte species and the reference species as taught by Merren into the modified method of Papac et al (Anal. Chem.) because Merren shows that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances, thereby permitting single channel processing of the combined signal.

Double Patenting

7. Claims 31 and 37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31-50 of copending Application No. 09/024,988. Although the conflicting claims are not identical, they are not patentably distinct from each other because although the claims of application 09/808,314 do not require that the IRS is modified analyte with shifted molecule weight as independent claim 31 in application 09/024,988 one of ordinary skill would recognize that the claims of 09/024,988 would encompass claims of 09/808,314.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

8. Applicant's arguments filed May 25, 2005 have been fully considered but they are not persuasive.

Applicant argues that the capturing and isolating of at least one or more analyte is performed completely differently than the process described in Papac. In particular,

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Papac fails to disclose releasing an isolated analyte species by alerting the analyte species from an antibody and then detecting the presence of the isolated and released analyte species. Applicant argues that in contrast in Applicants' invention, the analyte species is released by eluting it from the antibody and a released analyte species is detected using mass spectrometer to determine whether the analyte species is present in the physiological specimen. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the analyte species is released by eluting it from the antibody and a released analyte species is detected using a mass spectrometer to determine whether the analyte species is present in the physiological specimen) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that the Gaskell reference specifically states that "the success of the detection procedure was dependent on both the selectivity of tandem MS detection and on the achievement of a sufficiently "clean" biologic extract by Immunoabsorption." Accordingly, the Gaskell reference cited by the Examiner actually teaches away from the instantly claimed invention by using tandem MS for quantification. Applicant states that different mass spectrometric measurements were taken of similar portions of the same serum extract and compared. In contrast, Applicants' instantly claimed invention, the analyte and IRS are measured using MS in a single measurement. Accordingly, it would not have been obvious to one of ordinary

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skill in the art to incorporate the method disclosed in Gaskell into the method of Papac to arrive at Applicants' claimed invention because Applicants' claimed invention would then require tandem MS and Applicants' claimed invention requires single dimension MS. This is not found persuasive because as stated in the previous office action the Examiner has not relied upon Gaskell for teaching tandem MS, but rather has relied upon Gaskell for teaching that it is known in the art to incorporate internal references into a sample for the quantification of an analyte. The primary reference (Papac et al) clearly teaches the use of MALDI/TOF (single dimension) (same as used by Applicant) in a method for the detection of analyte and the secondary reference (Gaskell) teaches the incorporation of an internal standard in methods to provide for the quantification of an analyte. Also, as stated in the previous office action, it would have been obvious to incorporate an internal standard and also develop a standard curve for quantification analyses into the method of Papac et al (Anal Chem). Because Gaskell teaches that the addition of an internal standard provides for precise and accurate data and provides for the quantification of an analyte of interest. Thus, Examiner has not relied upon Gaskell for the steps of quantification but rather has relied upon Gaskell for teaching that it is known in the art to use internal standards to develop a standard curve which provides for the quantification of an analyte. Therefore, one of ordinary skill in the art would understand that the incorporation of a standard curve in the method of Papac et al provides for the quantification of an analyte. Therefore, the combination of Papac et al and Gaskell teach a single dimension mass spectrometric process for quantifying an analyte.

Applicant argues that the Papac reference fails to disclose the use of combining an internal reference species with a specimen, capturing and isolating an analyte and the internal reference species contained in the specimen and quantifying the analyte using single dimension mass spectrometric analysis to resolve signals for the analyte and the internal reference species to determine the amount of the captured analyte and that the Gaskell reference fails to disclose using single dimension mass spectrometry and instead requires using tandem mass spectrometry for detecting an analyte and internal standard and for quantifying the analyte. This is not found persuasive because of reasons stated above that the combination of Papac and Gaskell teach these claimed limitations and that the combination of the references is proper. Applicant further argues that Chiabrando discloses a method which utilizes gas chromatography-mass spectrometry and Chiabrando fails to disclose the use of single dimension mass spectrometry to analyze and quantify an analyte. This is not found persuasive because the Examiner has not relied upon Chiabrando for teaching these limitations but rather has relied upon Papac and Gaskell for teaching these limitations. The examiner has relied upon Chiabrando for teaching that it is known in the art to combine a plurality of distinctive internal reference species to a sample. Also, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that Merren fails to disclose single dimension mass spectrometric analysis of an analyte and an internal reference species using a standard single beam mass spectrometer. This is not found persuasive because Examiner has not relied upon Merren for teaching single dimension mass spectrometric analysis but rather has relied upon the combination of Papac et al. Gaskell and Chiabrando for teaching this limitation. Examiner has relied upon Merren for teaching interpolating the analyte species mass spectrometric response to the IRS's mass spectrometric response. Therefore, it is the Examiner's position that the combination of references is proper and reads on the instantly recited claims.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Gary Counts
Examiner
Art Unit 1641
July 29, 2005



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08/03/05